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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,875	08/13/2002	John L Teem	FSU -100C2XC1	1427

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,875	TEEM, JOHN L	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *14-31,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 32-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-13 and 32-57) in the reply filed on January 10, 2005 is acknowledged.

Claims 14-31, 58 and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 10, 2005.

Information Disclosure Statement

The information disclosure statements filed October 7, 2002 and October 12, 2004 have been considered, and a signed and initialed copy of the form PTO-1449s are attached to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zerhusen *et al.* (*J. Biol. Chem.* **247**: 7627-7630, March 1999; see entire document; henceforth Zerhusen) in view of Fields *et al.* (US 5,667,973; see entire document, henceforth Fields).

Fields teaches a method for determining protein-protein interactions (see for example the Abstract) by a yeast two-hybrid system. The method involves the construction of two "hybrid" genes, wherein a first protein to be tested for interaction is fused in frame with a DNA-binding domain, and a second protein to be tested for interaction is fused in frame with a transcriptional activation domain (see for example column 3, lines 18-33). When two proteins that interact are tested, their interaction brings the DNA binding and transcriptional activation domains into proximity, allowing them to initiate the transcription of a marker gene that can be easily detected (see for example column 3, lines 18-33). In specific embodiments, these "hybrid" genes are expressed in yeast cells, such as *S. cerevisiae* (see for example column 4, lines 14-18); thus host cells comprising such hybrid genes are taught by Fields. In certain instances, the DNA binding domain and transcriptional activation domains are generated from the yeast GAL4 protein (see for example column 4, lines 53-56). Additionally, the reconstituted transcription factor (i.e., the DNA binding and transcriptional activation domains) drives the expression of a marker gene such as lacZ, which can be easily detected (see for example column 6, lines 41-46). Although Fields teaches the general principle behind using "hybrid" genes for investigating the interaction of proteins in general, there is no specific disclosure for using CFTR polypeptides in the assay described by Fields.

Zerhusen teaches that the CFTR protein is a transmembrane chloride channel that, when mutated, leads to defective regulation/transport of chloride ions and results in the development of cystic fibrosis (see for example the introductory paragraph on page 7627). It is noted that cystic fibrosis is a highly prevalent human affliction. Importantly, Zerhusen teaches that intra and intermolecular interactions between CFTR polypeptides are responsible for the formation of

CFTR dimers, which then form proper chloride channels (see for example the Abstract and the first paragraph of page 7627, right side). Indeed, Zerhusen demonstrates the need for intermolecular interactions between CFTR polypeptides (i.e., interactions between two CFTR polypeptides) in order to form effective chloride channels by showing that the covalent linkage of wildtype CFTR polypeptides leads to normal chloride conductance, while the linkage of wildtype and mutant (i.e., disease state-asssociated) CFTR polypeptides gives intermediate chloride conductance (see for example the Abstract and Figure 2). Thus, Zerhusen teaches that it is important to characterize the interaction between CFTR polypeptides for the purpose of understanding the pathology of cystic fibrosis.

It would have been obvious to combine the teachings of Fields and Zerhusen to develop a method of determining the interactions between CFTR polypeptides because both teachings involve studying the effects of polypeptide interactions on the function of polypeptides. Fields studies the interaction of polypeptides in general, whereas Zerhusen studies the interaction of a specific pair of CFTR polypeptides; this is effectively a species genus relationship. The ordinary skilled artisan would be motivated to combine the teachings of Fields and Zerhusen in order to further characterize the interaction of CFTR polypeptides, which is demonstrated by Zerhusen to have important ramifications on the pathology of cystic fibrosis, a high profile human disease. By using the methods of Fields, the ordinary skilled artisan will have the benefit of characterizing the effects of CFTR polypeptide interactions without the need for covalently linking the polypeptides, giving them a more native environment for studying said interactions. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the methods taught by Fields with the CFTR

polypeptides as taught by Zerhusen because it is merely a substitution of a specific polypeptide (CFTR) for a general polypeptide (as taught in the methods of Fields).

Claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54, 57 and 4*, 35* and 48* are rejected under 35 U.S.C. 103(a) as being unpatentable over Zerhusen and Fields (as applied to claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54 and 57 above), and further in view of Payan *et al.* (US 6,316,223; see entire document; henceforth Payan). Note- "*" indicates those claims specifically rejected by the new combination of references.

Zerhusen and Fields teach all of the limitations as set forth in the rejection of claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54 and 57 above. Briefly, Zerhusen and Fields teach a method for the characterization of CFTR polypeptide interactions using a yeast two-hybrid system. However, Zerhusen and Fields, while teaching the use of yeast cells to explore these interactions, do not teach using mammalian cells for the same purpose.

Payan teaches a method for determining protein interactions in mammalian cells, specifically stating that the mechanism is similar to the yeast two-hybrid system (see for example the bridging paragraph of columns 3-4). Thus, Payan teaches that the principles of the two-hybrid system (such as those taught by Fields) are applicable in mammalian cells as well.

It would have been obvious for the ordinary skilled artisan to practice the methods of Zerhusen and Fields in mammalian cells because, as Payan specifically indicates, the principles of the yeast two-hybrid system are equally applicable in mammalian cells. Thus, the use of yeast or mammalian cells is merely an obvious substitution. The ordinary skilled artisan would have been motivated to use mammalian cells for examining the interaction of CFTR polypeptides

because mammalian cells offer the advantage of being the native environment for the expression, folding and function of CFTR polypeptides. Since these interactions are important for characterizing the pathological implications of the interactions, the ordinary skilled artisan would obviously want to determine the interaction in the most native environment to establish physiologically relevant results. Absent evidence to the contrary, and given the statement by Payan that the yeast and mammalian two-hybrid systems are equivalent, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the methods of Zerhusen and Fields in mammalian cells.

Claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54, 57 and 11-12*, 42-43* and 55-56* are rejected under 35 U.S.C. 103(a) as being unpatentable over Zerhusen and Fields (as applied to claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54 and 57 above), and further in view of Neville *et al.* (IDS reference R16; see entire document; henceforth Neville). Note- "*" indicates those claims specifically rejected by the new combination of references.

Zerhusen and Fields teach all of the limitations as set forth in the rejection of claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54 and 57 above. Briefly, Zerhusen and Fields teach a method for the characterization of CFTR polypeptide interactions using a yeast two-hybrid system. However, Zerhusen and Fields, while teaching the examination of both wildtype and mutant CFTR polypeptide interactions, does not specifically teach the examination of the ΔF508 CFTR mutation (which is a mutation in the NDB1 domain).

Neville teaches that significant protein-protein interactions occur at the NBD1 domain (see for example the first full paragraph of the left side of page 2402), and can be affected by the ΔF508 CFTR mutation.

It would be obvious for the ordinary skilled artisan to measure the interaction of CFTR polypeptides having the ΔF508 mutation because the domain in which the mutation occurs has significant effects on protein-protein interactions, as stated by Neville. Furthermore, it is well known that this mutation is the most prevalent among mutations found in patients suffering from cystic fibrosis. Thus, it would be obvious to test those mutations that were relevant to the pathological state when characterizing the interaction of proteins involved in said state. The ordinary skilled artisan would have been motivated to test the effects of the ΔF508 mutation on CFTR polypeptide interactions because of its prevalence in the pathological state of cystic fibrosis. In other words, it would be obvious to test the interaction of the mutant that is most frequently found in the diseased state in order to determine the relevance of CFTR protein-protein interactions on the development of cystic fibrosis, which is the purpose of the teachings set forth in Zerhusen and Fields. Indeed, the teachings of Zerhusen and Fields do examine the effects of CFTR mutants that give rise to abnormal function. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when substituting the ΔF508 mutant for one of the mutants tested in the methods of Zerhusen and Fields.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JAMES KETTER
PRIMARY EXAMINER